

### **Remarks**

Applicants have amended the claims to further clarify the claimed invention, and to present the claims in condition for allowance.

Claim 35 has been amended to clarify that "vitamin D" as used in Claim 35 does not include a hydroxylated vitamin D or hydroxylated vitamin D metabolite.

Claims 67 and 68 have been amended to clarify that "vitamin D" as used therein refers to vitamin D<sub>2</sub> or D<sub>3</sub>.

Applicants submit no new matter has been added by these amendments. Support for these amendments can be found, for example, at pages 4 and 47 of the specification.

### **I. Examiners' Request for Additional Information**

Applicants thank the Examiners for their efforts to advance this case to allowance. As suggested during the interview of August 10, 2004 with Applicants' representatives, Applicants provide herewith additional information to distinguish their claimed invention over Neer et al. (U.S. Patent 4,698,328, hereinafter "Neer").

#### **A. Neer teaches co-administration of PTH(1-34) with a hydroxylated vitamin D compound**

Applicants' claims are patentably distinct over Neer at least for the reason that Neer teaches co-administration of PTH(1-34) with 1,25 OH vitamin D, or some other hydroxylated vitamin D metabolite. Neer does not teach co-administration with vitamin D, according to Applicants' amended claims.

Applicants have amended their claims such that "vitamin D," as used in the amended claims, does not include hydroxylated vitamin D or hydroxylated vitamin D metabolites, and one of skill in the art would understand that vitamin D and hydroxylated vitamin D are distinct compounds with distinct activities (See attached declaration of Hunter Heath, M.D.). Claim 35 has been amended to specifically proviso out hydroxylated vitamin D and hydroxylated vitamin D metabolites. Claims 67 and 68 have been amended to specify that vitamin D means supplemental vitamin D<sub>2</sub> or D<sub>3</sub>.<sup>1,2</sup>

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<sup>1</sup>"Vitamin D: any or all of several fat-soluble vitamins chemically related to steroids, essential for normal bone and tooth structure, and found esp. in fish-liver oils, egg yolk, and milk or produced by activation (as by ultraviolet irradiation) of sterols: as a: CALCIFEROL b: CHOLECALCIFEROL – called the sunshine vitamin.

Vitamin D<sub>3</sub>: CHOLECALCIFEROL

Therefore, Applicants' amended claims are not directed to co-administering PTH(1-34) with 1,25 OH vitamin D or hydroxylated vitamin D metabolite, as disclosed by Neer. Applicants claim administration of 20 ug/day hPTH(1-34) without coadministering an antiresorptive agent, other than vitamin D and calcium.

Applicants submit their claims are novel and non-obviousness over Neer at least for the reason that Neer discloses co-administration of PTH(1-34) with 1, 25 OH vitamin D, and does not teach or suggest co-administering PTH(1-34) with vitamin D.

B. Neer provided no motivation to choose Applicants' claimed dose

Neer teaches a broad dose range for PTH(1-34) of 100-700 units per day. There is no basis in Neer for selecting Applicants' claimed dose of 20 ug/day. According to the declaration submitted herewith by Dr. Hunter Heath, there "would have been no basis, instruction, or motivation for selecting Lilly's specific dose of 20 ug/day" based on the information taught in Neer.

Neer lacks information as to the corresponding dose range in micrograms. The uncertainty in Neer's dose is compounded by the high degree of imprecision in bioassays including PTH assays. As stated in Dr. Heath's declaration, "It is very difficult to know the mass of peptide corresponding to a given bioassay estimate, mainly because the precision of such assays is intrinsically poor. For a given amount of standard the biopotency estimates using a given assay (e.g. chick hypercalcemia) may vary over a ten-fold range. Assay precision is even worse depending on the operator, the standard chosen, the particular laboratory, or the source or diets of the animals used."

As a consequence, a skilled artisan following Neer's teaching would not have been motivated to choose Applicants' claimed dose of 20 ug/day.

C. Applicants' claimed dose provided unexpected advantages

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Vitamin D<sub>2</sub>: CALCIFEROL

Merriam-Webster's Medical Desk Dictionary.

<sup>2</sup> Vitamin D occurs naturally in a variety of foods and is readily available as a dietary supplement. Vitamin D itself is biologically inert and remains so until hydroxylated in the kidney and liver to produce 1,25 dihydroxylated vitamin D. The dihydroxylated form of vitamin D is responsible for maintaining normal serum calcium levels, in part by increasing the efficiency with which the intestine absorbs dietary calcium. See e.g. M.F. Holick, "Vitamin D: photobiology, metabolism, mechanism of action and clinical applications", In Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 4<sup>th</sup> Ed. M. Favus Ed. Lippincott Williams & Wilkins, 1999.

Applicants' clinical trials established a limited dosage range within which PTH(1-34) would be safe and effective. Unlike Neer, Applicants discovered and claim that 20 ug/day reduced the risk of vertebral and nonvertebral bone fracture. Prior to Applicants' invention there was no evidence of reduced fracture associated with administration of PTH without concurrent administration of an antiresorptive agent other than vitamin D or calcium. Neer's patent did not teach or suggest that administration of PTH would reduce the risk of vertebral and non-vertebral bone fracture. Neer showed increased BMD *at the spine* but reported *no change in BMD at a cortical site*. Thus, even *if* there were a strong correlation between increased BMD and reduced fracture (which is not the case; See Heath declaration), Neer would have provided no reasonable basis to expect reduced fracture at *both* vertebral and nonvertebral sites.

In addition to discovering that a dose of 20 ug/day is effective in reducing the risk of bone fracture, Applicants discovered that these effects can be achieved with a decrease in certain undesirable side effects (See specification at page 52, and Heath declaration). According to the attached article supported by Lilly and published in the New England Journal of Medicine, 40 ug/day of Lilly's PTH(1-34) "was more likely to have side effects" and more likely to result in patients being withdrawn from this particular study due to an adverse event (6% of patients withdrew in the placebo and 20 ug/day dose groups while 11% of patients withdrew in the 40 ug/day dose group). NEJM, 2001, 344 at 1434 and 1438.

For example the incidence of hypercalcemia is stated to have occurred in 3% of women receiving 20 ug/day and 11% of women in the 40 ug/day dose group. Treatment was withdrawn because of repeatedly elevated serum calcium concentrations in one woman in the 20 ug/day group compared to nine in the 40 ug/day group. Id. at 1439. The Examiner is encouraged to read this article, especially the Adverse Events section beginning on page 1437.

In addition, according to the Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document (attached and available at: [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2\\_01\\_lilly.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_01_lilly.pdf); cited herein), "There were significant increases in the incidence of headaches and nausea compared with placebo that were consistent with previous studies evaluating doses higher than 20 ug/day." See pages 93 -94.

## II. Response to the Pending Rejection

The pending rejection alleges that Applicants' claimed dose is anticipated by Neer. Alternatively, the rejection alleges that Applicants' claims are obvious over Neer. Following are Applicants' specific comments in response to the rejection.

### 1. Neer fails to teach Applicants' claimed dose

The Examiner concedes that "there is no art-accepted conversion of units to ug for hPTH1-34." However, "the claimed daily dose of 20ug [is] . . . *consistent with the prior art.*"(emphasis added).

Applicants challenge the relevance of the Examiner's statement. The correct standard for anticipation is, and always has been, that a single prior art reference must clearly and unambiguously teach each and every element of the claimed invention, either expressly or inherently.

Anticipation requires a comparison of the elements of the claimed invention with the prior art. Respecting drug dosages, one cannot directly compare "units of activity" with microgram quantities. It is axiomatic that conversion between units of measure cannot take place without a reliable standard and an agreed upon conversion relationship. Thus, for example, by established convention there are 2.54 centimeters per inch, and 454 grams per pound. In such "static" cases, there is no difficulty in converting one unit of measure to another. However, conversion problems are not always so straight forward. For example, converting from Dollars to Euros requires application of a conversion factor that varies over time. Such "floating" conversion problems are not standardized in the same sense as the static cases. In practice this means that "floating" conversion problems require knowledge of the precise value of the conversion factor each time a conversion is made. The "floating" conversions are analogous to the issue in this case.

The allegation that Neer anticipates Applicants' claimed dosage requires comparison of Neer's dosage, specified in units of activity, with Applicants' claimed dosage, specified in micrograms. However, since the unit of measure disclosed by Neer ("Units") differs from that claimed by Applicants ("micrograms"), and because of the reasons stated above, direct comparison cannot be made.

The Examiner argued that Neer's dosage could be "converted" to micrograms, (1) "by searching the art" or (2) "by simply performing the chick hypercalcemic assay to

determine the conversion factor from units to ug.” (Page 7, Office Action). Neither of these proposals is tenable, on legal or technical grounds.

Under the first proposal, the Examiner imported specific activity values from other references. The law on anticipation is clear – only a single reference can serve as basis for an anticipation. The law does not permit combining references, nor importing substantive information into an allegedly anticipatory reference, except to “explain” a primary reference, but never *to add information that is not already in the primary reference*. Neer does not contain the information the Examiner wishes to incorporate. As such, the Examiner’s action goes beyond “explaining” Neer, and violates the limitations of a proper anticipation.

Under the second argument, the Examiner asserted that Neer can be converted “simply [by] performing the chick hypercalcemic assay to determine the conversion factor from units to ug.” (Page 7, Office Action). Applicants disagree.

Determination of the “conversion factor” cannot be made by the method proffered by the Examiner. Without access to the *particular standard* stipulated by Neer there is no reliable way to convert *Neer’s* units to the corresponding micrograms, nor to compare another sample of PTH(1-34) against Neer’s disclosure. For example, a measurement of “X” units of activity in the chick assay would translate to a *set* of potential values for the microgram quantity, depending on the particular standard used and its specific activity.

Drs. Micklejohn and Griffiths submitted declarations stating that the PTH(1-34) standard stipulated by Neer does not exist. Since the standard specified by Neer is not available, there is no reliable way to compare the potency of a sample of PTH(1-34) with the potency of Neer’s PTH. In short, the experiment proposed by the Examiner cannot be performed to achieve the stated result, namely the conversion of Neer’s dosage from units to micrograms.

## 2. Applicants’ post-filing date publication cannot be grounds for anticipation

The Examiner refers to Applicants’ own post-filing date publication (Neer et al. NEJM, 344, 1434-1441, 2001) as support for his position. This reference is not prior art. The Examiner states that the NEJM paper teaches “use of the daily dose of 20 ug PTH(1-34) for treatment of osteoporosis and reduction of bone fracture in postmenopausal women with osteoporosis.” Aside from the fact that the 2001 NEJM paper is not prior

art, there is no basis whatsoever to deduce, or infer *any* connection or correlation between the dosage disclosed in the NEJM paper and the cited Neer reference.

Applicants respectfully request withdrawal of the rejection.

3. Neer fails to teach reduced fracture

The Examiner concludes that Neer “inherently teach[es] reducing the risk of bone fracture.” (Office Action, p 8). Further, “Since Neer et al. teach treatment of osteoporosis with hPTH1-34, Neer et al inherently teach reducing the risk of bone fracture.”

Even *if* the foregoing statement were logically sound, which is rebutted in the following discussion, it would fail to establish anticipation. Applicants’ claims are novel regardless of whether fracture reduction is inherent in Neer. Neer *utterly fails* to anticipate the claimed invention, at least because it fails to disclose Applicants’ claimed dosage, and/or that PTH could be administered without an antiresorptive agent, or in combination with vitamin D to effectively treat osteoporosis.

Applicants challenge the assertion that Neer “inherently teach[es] reducing the risk of bone fracture.” The Examiner states that since Neer teaches “treatment of osteoporosis with hPTH 1-34” it “inherently teach[es] reducing the risk of bone fracture.” This conclusion does not follow from the premise.

The mere fact that an agent is designated a “treatment for osteoporosis” does not mean that it must therefore reduce bone fracture. An example of this is fluoride, an agent that has been used as a therapy for osteoporosis and which substantially increases BMD, yet without any beneficial effect on fracture incidence.

In sum, Applicants’ claims are novel over Neer at least because: (1) Neer fails to teach the claimed dose (20 ug/day), and (2) Neer fails to teach that hPTH(1-34) could be administered to osteoporosis patients to reduce the risk of vertebral and nonvertebral bone fracture.

**Applicants’ claimed invention is non-obvious over Neer**

The Patent Office has the burden of establishing a *prima facie* case of obviousness. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). A showing of *prima facie* obviousness requires that (1) the prior art must disclose or suggest the modification that is required for arriving at the invention, and (2) the prior art must provide one skilled in the art a reasonable expectation of success if the modification is made. See *In re Vaeck*,

20 USPQ2d 1438 (Fed. Cir. 1991). *Prima facie* obviousness requires consideration of the prior art as a whole, including any references that would “teach away” from the claimed invention. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988).

The rejection states:

“The Examiner’s position is evidenced by the prior art of record. For example, Lindsay et al. (The Lancet, 350:550-555, 1997) teach that treatment of postmenopausal women with osteoporosis with hPTH(1-34) in a daily dosage of 25 ug increased total-body bone mineral and that the increased vertebral mass was associated with a reduced rate of vertebral fracture. Lindsay et al. further teach that bone-mass changes may be consistent with a reduction in all osteoporotic fractures (page 550, right column). Cosman et al. teach that hPTH(1-34) increases bone mass and perhaps a reduction in osteoporotic fracture (Abstract). Hirano et al teach that hPTH(1-34) enhances the mechanical strength of cortical bone in rabbits (abstract). Furthermore, Turner et al. teach hPTH(1-34) induces parallel increases in bone mass and bone strength in animals, which is clearly cited in the the [sic] article of N Engl J Med 344:1434-1441, 2001.”

The Examiner’s remarks do not explain how Neer allegedly would have suggested Applicants’ claimed invention, nor how one skilled in the art following Neer’s teaching would have had a reasonable expectation of arriving at Applicants’ claimed invention. As such, the rejection fails to establish a *prima facie* case. Applicants respectfully request withdrawal of the rejection.

In the following sections, Applicants argue that even *if* a *prima facie* case had been made (something Applicants dispute) the claimed invention would not have been obvious over Neer, or any other reference mentioned by the Examiner.

1. Applicants’ invention was surprising and unexpected

Prior to Applicants’ disclosure, there were substantial fears associated with the safety and efficacy of administering PTH in the absence of an antiresorptive agent for the treatment of osteoporosis. The earliest trial in humans raised a red flag when the data showed that while PTH increased bone volume at a trabecular-rich site, it also induced a *loss* of mineral from cortical bone. Thus, when administered alone, PTH appeared to *steal* mineral from cortical bone while building bone at the spine and other non-cortical sites. This phenomenon came to be known as “robbing Peter to pay Paul.” (See Reeve et al., 1980; IDS Ref CO)

The early observations lead to the fear that loss of bone mass at cortical sites in response to treatment with PTH might *harm* patients by *increasing* the risk of fracture at

such sites.

Later work in the field took these concerns seriously, and moved away from PTH-alone regimens, toward co-administering PTH with an antiresorptive agent, such as estrogen, or in the case of Neer, with hydroxylated vitamin D derivatives.<sup>3</sup>

Applicants' discovery represents a break-through that ran counter to the teachings in the art. Applicants showed, contrary to the evidence in the prior art, that PTH could *safely* be administered to patients *without co-administration of antiresorptive agents other than vitamin D or calcium*. Moreover, Applicants showed that PTH administered in the absence of antiresorptive agents significantly reduced the risk of bone fracture *throughout* the skeleton.

## 2. Fracture reduction was unexpected in view of the teachings in Neer

The 1980 Reeve et al. paper (IDS Ref CO; Neer was a co-author) showed increased trabecular bone volume, but negative calcium balances. Reeve et al. proposed several measures to overcome this serious limitation in the clinical utility of PTH as a therapy for osteoporosis. First, Reeve et al. proposed "a regimen in which treatment is cyclically interrupted so that the prolonged period of osteoblastic activity after each period of activation is unopposed by excess osteoclasts." (Id.) Second, Reeve et al. proposed "this hormone fragment might best be used in combination with oestrogen, calcitonin, a diphosphonate, or some other agent that will limit resorption while allowing bone formation to continue." (Id.).

Following Reeve et al. (1980), most, if not all, trials co-administered PTH with an antiresorptive agent, or with an agent that would improve calcium balance. Throughout the 1980s, Neer's group published multiple papers that taught that PTH would only be effective in building bone mass when co-administered with 1,25(OH)<sub>2</sub>-vitamin D. (cf. Neer et al. patent; IDS Refs CS and CT).

Neer's patent did not teach or suggest that administration of PTH would reduce the risk of vertebral and non-vertebral bone fracture. While the Neer patent showed increased BMD *at the spine* of male patients, it reported *no change in BMD at a cortical site*. Thus, even if there were a strong correlation between increased BMD and reduced

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<sup>3</sup> Multiple references have been cited in Applicants' IDS that describe the concern and advocate combined regimens. See e.g. IDS References CO, CP, CAF, CR, CX, CZ, CAB, CS, CT, CV, CQ, CB and CF.

fracture (which is not the case; See Heath declaration), Neer would have provided no reasonable basis to expect reduced fracture at *both* vertebral and nonvertebral site.

In view of Neer's findings respecting the impact of PTH at nonvertebral bone, showing either *no change* in BMD (Neer patent; in males), or a *decline* in BMD (cf., IDS ref CY, in postmenopausal women), there would have been *no reasonable basis* to expect that PTH would reduce the risk of bone fracture at both vertebral *and* nonvertebral sites.

3. Lindsay et al. taught administration of PTH plus estrogen

The Examiner mentioned Lindsay *et al.* (IDS Ref CB) as "evidence" for his position. According to the Examiner, Lindsay showed an "increased vertebral mass [that] was associated with a reduced rate of vertebral fracture." The Examiner further states, "Lindsay et al. teach that treatment of postmenopausal women with osteoporosis with hPTH(1-34) in a daily dose of 25 ug increased total-body bone mineral . . . ."

However, Lindsay et al. taught *co-administration of PTH(1-34) plus estrogen*. The Lindsay et al. patients were given two powerful bone agents at the same time and there is no way to separate their effects.

While Lindsay et al. suggests that patients who received PTH plus estrogen *may have* experienced a reduced risk of vertebral bone fracture, the data were not significant at the 20% height reduction level that is most often reported as evidence of vertebral fracture. Moreover, the study was insufficiently powered to address this question.

Applicants submit that Lindsay's disclosure did not disclose, nor would it have suggested, Applicants' claimed invention. The teachings of Lindsay et al. were in line with other references published prior to Applicants' filing date, namely toward co-administration of PTH with an antiresorptive agent such as estrogen, or with 1,25 (OH)<sub>2</sub> D.

4. Cosman, Hirano, and Turner

The Examiner mentions three additional references:

Cosman et al. teach that hPTH(1-34) increases bone mass and perhaps a reduction in osteoporotic fracture (Abstract). Hirano et al. teach that hPTH(1-34) enhances the mechanical strength of cortical bone in rabbits (abstract). Furthermore, Turner et al. teach hPTH(1-34) induces parallel increases in bone mass and bone strength in animals, which is clearly cited in the the [sic] article of N Engl J Med 344:1434-1441, 2001.


Citations for the Cosman and Hirano references were not provided in the present Office Action. In this response, Applicants will assume they correspond to art cited in Applicants' IDS. The Cosman et al. reference (Cosman and Lindsay; IDS Code CF) is a review article that clearly relates to an earlier study by the same authors in which PTH was *co-administered* with estrogen. As previously argued respecting the Lindsay et. al. study, results achieved by co-administration of PTH plus estrogen cannot be extrapolated to PTH-alone. For at least this reason, Cosman et al. does not impugn the patentability of Applicants' claimed invention.

Hirano et al. (IDS Code CA) reported that hPTH(1-34) administered to *normal* (*i.e.* non-osteoporotic) rabbits substantially increased cortical BMD when administered at a daily dose of 10 ug/kg and 40 ug/kg for 140 days. Hirano showed a substantial dose-dependent increase in BMD in cortical bone of the femur of at least 20% over the control (See Fig. 2, p 541). Hirano's results clearly *differ* from the effects of PTH on cortical bone in osteoporotic humans. Many reports in the art show that administration of PTH to humans produces either no effect on cortical BMD, or a decline in BMD over control values. Thus, Hirano's data would not have been viewed by the skilled artisan as suggesting an effect in humans; to the contrary, Hirano would have apprised the skilled artisan of fundamental differences between rabbits and humans in their respective response to PTH.

Respecting Turner et al., J. Bone Miner Res., 14, Suppl 1, SA421 (Sep. 1999), Applicants note this paper published *after* Applicants' filing date, and therefore is not prior art. As such Turner et al. provides no basis for arguing against the patentability of Applicants' claimed invention.

Applicants respectfully submit the rejection has been overcome. Applicants request the Examiner withdraw the rejection and advance the case to issuance without further delay. Please feel free to contact the undersigned with any questions.

Respectfully submitted,



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